In a similar fashion, identification of mutations in CDK4 and/or CDK6 which effect binding to a CCR-protein can be used to identify potential peptidyl fragments of CDK4/CDK6 which can competitively bind a CCR-protein and interfere with its ability to inhibit the CDK. As described below, we have characterized a CDK4 mutant which abrogates binding by p15 and p16, and consequently becomes insensitive to inhibition by those CCR-proteins. This mutation, in fact, occurs in a stretch of amino acid residues which is conserved between CDK4 and CDK6. Accordingly, peptidomimetics based on this stretch might be useful as antagonists of CCR-proteins, in that they are expected to compete with CDK4 or CDK6 for binding to the CCR-protein. In a preferred embodiment, the CCR antagonist is a peptide or a non-peptide analog consisting of the amino acid sequence VAEIG(V/E)GAYG(T/K)V(F/Y)KARD (SEQ ID NO: 15), though more preferably a peptidomimetic consisting of the amino acid sequence V(F/Y)KARD (SEQ ID NO: 16), and even more preferably of the tetrapeptide consisting of the amino acid sequence KARD (SEQ ID NO: 17). These and other peptidyl portions of CDKs can be tested for binding to CCR-proteins such as p15 or p16 using, for example, the thioredoxin fusion protein constructs mentioned above.

The paragraphs presented above incorporate changes as indicated by the marked-up versions below.

In a similar fashion, identification of mutations in CDK4 and/or CDK6 which effect binding to a CCR-protein can be used to identify potential peptidyl fragments of CDK4/CDK6 which can competitively bind a CCR-protein and interfere with its ability to inhibit the CDK. As described below, we have characterized a CDK4 mutant which abrogates binding by p15 and p16, and consequently becomes insensitive to inhibition by those CCR-proteins. This mutation, in fact, occurs in a stretch of amino acid residues which is conserved between CDK4 and CDK6. Accordingly, peptidomimetics based on this stretch might be useful as antagonists of CCR-proteins, in that they are expected to compete with CDK4 or CDK6 for binding to the CCR-protein. In a preferred embodiment, the CCR antagonist is a peptide or a non-peptide analog consisting of the amino acid sequence VAEIG(V/E)GAYG(T/K)V(F/Y)KARD (SEQ ID NO: 15), though more preferably a peptidomimetic consisting of the amino acid sequence V(F/Y)KARD (SEQ ID NO: 16), and even more preferably of the tetrapeptide consisting of the

amino acid sequence KARD (SEQ ID NO: 17). These and other peptidyl portions of CDKs can be tested for binding to CCR-proteins such as p15 or p16 using, for example, the thioredoxin fusion protein constructs mentioned above.

In the claims:

Please cancel pending claims 11, 58, 61-64, 66, 68-70, 72-76, and 83-90 without prejudice. For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

Please add the following new claims.

91. (New) An antibody preparation specifically reactive with a 16 kD protein that co-precipitates with CDK4 from cell lysates of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody, wherein the molecular weight of the 16 kD protein is identified by polyacrylamide gel electrophoresis (PAGE) under denaturing conditions.

92. (New) An isolated antibody, or fragment thereof, specifically immunoreactive with a 16 kD protein that co-precipitates with CDK4 from cell lysates of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody, wherein the molecular weight of the 16 kD protein is identified by PAGE under denaturing conditions.

93. (New) The antibody of claim 92, wherein the antibody is a monoclonal antibody.

94. (New) An isolated antibody, or fragment thereof, specifically immunoreactive with a 16 kD protein that co-precipitates with CDK4 from cell lysates of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody, conjugated to a detectable label, wherein the molecular weight of the 16 kD protein is identified by PAGE under denaturing conditions.

95. (New) The antibody of claim 94, wherein the anti-p16 antibody is a monoclonal antibody.

96. (New) The antibody of claim 94, wherein the anti-p16 antibody is a Fab fragment.

97. (New) The antibody of claim 94, wherein the anti-p16 antibody is a $F(ab')_2$ fragment.

98. (New) A kit for detecting a cell cycle regulatory (CCR) protein comprising (i) an isolated anti-CCR antibody, or fragment thereof, specifically immunoreactive with a 16 kD protein that co-precipitates with CDK4 from cell lysates of SV40-transformed WI38 cells in the presence of an anti-CDK4 antibody, and (ii) a means for detecting the anti-CCR antibody in immunocomplexes with a CCR protein, wherein the molecular weight of the 16 kD protein is identified by PAGE under denaturing conditions.

99. (New) The kit of claim 98, wherein the means for detecting the anti-CCR antibody is a detectable label conjugated with the anti-CCR antibody.

100. (New) The kit of claim 98, wherein the means for detecting the anti-CCR antibody is a second antibody immunoreactive with the anti-CCR antibody.

101. (New) The kit of claim 98, wherein the anti-CCR antibody is a monoclonal antibody.

102. (New) The kit of claim 98, wherein the anti-CCR antibody is provided in a form suitable for detecting the cell cycle regulatory (CCR) protein in samples of cells.

103. (New) An antibody preparation specifically reactive with a p16 protein comprising SEQ ID NO: 35.

104. (New) An isolated antibody, or fragment thereof, specifically immunoreactive with a p16 protein comprising SEQ ID NO: 35.

105. (New) The antibody of claim 104, wherein the antibody is a monoclonal antibody.

106. (New) An isolated antibody, or fragment thereof, specifically immunoreactive with a p16 protein comprising SEQ ID NO: 35, and wherein the antibody is conjugated to a detectable label.

107. (New) The antibody of claim 106, wherein the antibody is a monoclonal antibody.

108. (New) A kit for detecting a cell cycle regulatory (CCR) protein comprising (i) an isolated anti-CCR antibody, or fragment thereof, specifically immunoreactive with a p16 protein

comprising SEQ ID NO: 35, and (ii) a means for detecting the anti-CCR antibody in immunocomplexes with a cell cycle regulatory (CCR) protein.

109. (New) The kit of claim 108, wherein the means for detecting the anti-CCR antibody is a detectable label conjugated with the anti-CCR antibody.

110. (New) The kit of claim 108, wherein the antibody is a monoclonal antibody.

111. (New) The kit of claim 108, wherein the means for detecting the anti-CCR antibody is a second antibody immunoreactive with the anti-CR antibody.

112. (New) The kit of claim 108, wherein the antibody is provided in a form suitable for detecting the cell cycle regulatory (CCR) protein in samples of cells.

REMARKS

Claims 91-112 (previous claims 11, 58, 61-64, 66, 68-70, 72-76, and 83-90) constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. The following was noted regarding the pending claims:

Claims 62 and 63 were listed as "Reiterated", yet included amended claim language, and were not entered. Secondly, the version of claim 68 examined in the Office Action mailed 11/21/01 was not the pending version of claim 68. The Examiner requested that the pending claims be canceled and a clean claim set be generated to establish the pending claim version.

Support for the method and conditions by which the molecular weight of the 16 kD protein can be found in Examples 1-2 and 5 of the instant specification.